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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,943	RUBINO ET AL.	
	Examiner	Art Unit	
	Gregg Polansky	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicants' amendments and Remarks/Arguments, filed 6/29/2007, in response to the Office Action filed on 4/4/2007, are acknowledged.

2. Applicants' cancellation of Claims 1-11 is acknowledged.

3. Claims 12-21 are under consideration.

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 103

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 12-21 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Azrolan et al. (U.S. Publication No. 2002/0013335), in view of Waranis et al. (U.S. Patent No. 5516770) and Haeberlin et al. (UK Patent Application Publication GB 2327611).

7. Claim 12 is drawn to a parenteral formulation comprising rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779), an alcoholic solvent, an antioxidant, a diluent solvent , and a surfactant. Claim 13 is drawn to the parenteral formulation of Claim 12 where the alcoholic solvent is ethanol or polypropylene (elected

species). Claim 14 is drawn to the parenteral formulation of Claim 12 where the antioxidant is d,l-α-tocopherol or citric acid (elected species). Claim 15 is drawn to the parenteral formulation of Claim 12 where the diluent solvent is ethanol or polyethylene glycol 400 (elected species). Claim 16 is drawn to the parenteral formulation of Claim 12 where the surfactant is polysorbate 80 (elected species). Claims 17 and 18 are drawn to the formulation of Claim 12, wherein CCI-779 comprises from about 1 mg/ml to about 25 mg/ml and from about 2.5 mg/ml to about 10 mg/ml respectively. Claim 19 is drawn to the parenteral formulation of Claim 12 wherein the antioxidant comprises from about 0.0005% to about 0.05% w/v of the formulation. Claim 20 is drawn to the parenteral formulation of Claim 12 wherein the surfactant comprises from about 0.5% to about 10% w/v of the formulation. Claim 21 is drawn to the parenteral formulation of Claim 12 wherein the solvent comprises from about 10 % to about 90% w/v of the formulation.

8. Azrolan et al. teach that rapamycin 42-ester with 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid (CCI-779) is a member of a group of compounds that are derivatives of the rapamycin nucleus (*see* Azrolan et al., paragraph 14). Azrolan et al. teach the parenteral administration of CCI-779 and other rapamycins and suggest a solvent of water, ethanol, glycerol, propylene glycol and polyethylene glycol or a combination thereof, a surfactant, such as hydroxylpropylcellulose, a preservative (*see* Azrolan, et al., paragraphs 28 and 29) and antioxidant (*see* Azrolan, et al., Claim 14). Additionally, Azrolan et al. teach and incorporate by reference preferred parenteral formulations of rapamycins taught by Waranis et al. (*see* Azrolan et al., paragraph 29).

Azrolan et al., do not teach a specific antioxidant (e.g., citric acid or d,l-α-tocopherol) or the surfactant, polysorbate 80. Also, Azrolan et al., do not teach the concentrations of CCI-779, antioxidant, surfactant, or solvent as specified in the claims of the instant application.

9. Waranis et al. teach an injectable rapamycin solution comprised of a mixture of a concentrate of rapamycin in propylene glycol with a diluent of polyethylene glycol 400 and a polyoxyethylene sorbitan ester (e.g., polysorbate 80) and water (*see* Examples 1-3), yielding an injectable formulation concentration of rapamycin of 0.2 mg/ml to 4 mg/ml (*see* column 2, lines 44-47), with 0.07-9.5% polysorbate 80 and 12-87% glycols (*see* column 3, lines 29-54). These concentrations are within the concentration ranges specified in the claims of the instant application.

Waranis et al. do not teach use of an antioxidant. Waranis et al. teach formulations of rapamycins, but not CCI-779 specifically. However, Azrolan et al. teach formulations disclosed by Waranis et al. as preferred parenteral formulations for CCI-779 (*supra*).

10. Haeberlin et al. teach the use of various carboxylic acids to stabilize (i.e., preserve) oral and parenteral formulations of macrolides, preferably a rapamycin. The preferred acids include malonic acid, oxalic acid, citric acid, and lactic acid (*see* page 4, lines 15-22). Haeberlin et al. teach a 0.05% to 5% acid concentration range (which encompasses the instant invention citric acid concentration specification) and further discloses that the preferred amount of acid may be determined by routine experimentation. Haeberlin et al. give as an example, a formulation of a rapamycin with

ethanol, Cremophor® EL (a surfactant), and citric acid. They present other examples of rapamycin formulations which include the use of 1,2 propylene glycol as a solvent and d,l-α-tocopherol as an antioxidant.

11. It would have been obvious to one of ordinary skill in the art at the time of the invention, who was motivated to produce a parenteral formulation of CCI-779, to combine the teachings of Azrolan et al., which discloses the essential elements of said formulation, with those of Waranis et al. and Haeberlin et al., which teach individual elements of Azrolan et al. in more detail. Waranis et al. teach the concentrations of the solvents (e.g. propylene glycol and polyethylene glycol 400), rapamycin, and a specific surfactant (polysorbate 80) for a parenteral rapamycin formulation. Haeberlin et al. teach the use of citric acid and d,l-α-tocopherol as a stabilizer in a rapamycin parenteral formulation. The Azrolan et al. teaching of including an antioxidant and preservative in rapamycin formulations, would motivate one to combine Azrolan et al. with Haeberlin et al. One would have been motivated to combine Azrolan et al. and Waranis et al., since Azrolan et al. specify and incorporate by reference the parenteral formulations of Waranis et al. One would have been motivated to perfect a parental formulation of CCI-779 to reduce the bioavailability uncertainties of other forms of administration (e.g. oral), leading to more accurate and reproducible doses of the agent.

Response to Arguments

12. Applicants' amendments of the Abstract, Specification, and Claims (see page 8), in response to the Specification and Claim objections of the previous Office Action (filed 4/4/2007) are acceptable and the objections have been withdrawn.

13. Applicants' arguments see page 9, Claims Rejections - 35 USC §102, with respect to instant Claims 12, 13, and 15 have been fully considered and are persuasive. The rejection of instant Claims 12, 13, and 15 under 35 USC §102 has been withdrawn.

14. Applicants' arguments, see pages 9-10, Claims Rejections - 35 USC §103, with respect to instant Claims 12-21, have been fully considered and are not persuasive. Applicants argue that "Azrolan does not describe a single parenteral formulation which comprises CCI-779, an alcoholic solvent, and antioxidant, a diluent solvent, and a surfactant and that Waranis and Haeberlin add nothing to Azrolan that would lead one of skill in the art to the present formulations". Although Azrolan does not teach a single parenteral formulation which comprises CCI-779, an alcoholic solvent, and antioxidant, a diluent solvent, and a surfactant, they do teach all of the components. Furthermore, as state in the rejection, Azrolan teaches (and incorporates by reference) the rapamycin formulation of Waranis as a preferred parentaeral formulation for CCI-779. The formulations taught by Waranis comprises a concentrate of rapamycin in propylene glycol (an alcoholic solvent), a diluent of polyethylene glycol 400, and a polyoxyethylene sorbitan ester surfactant (e.g. polysorbate 80). An antioxidant, selected from citric acid glycine, d,l-α-tocopherol, BHA, BHT monothioglycerol, ascorbic acid, or propylgallate, is the only formulation component recited by the instant claims missing from this

formulation. However, as acknowledged in Applicants' arguments, Haeberlin describes the "stabilization of rapamycins and ascomycins (e.g., FK-506) by formulation in acid , including malonic acid, oxalic acid, *citric acid* and lactic acid". In response to Applicants' argument that teachings of Haeberlin "does not recognize the benefit of antioxidants over acids generally in stabilizing macrolides", the fact that Applicants have recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Furthermore, it is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). In the instant invention, the Applicants must show that the teachings of the Haeberlin (i.e., the use of, *inter alia*, citric acid to stabilize a rapamycin formulation) do not work through the instant invention mechanism of an antioxidant] There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary

feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). Additionally, one of ordinary skill in the art would recognize that citric acid as taught by Haeberlin (as a stabilizer) is an antioxidant, and would satisfy the suggestion of Azrolan to add an antioxidant to their formulation.

Finally, In response to the Applicants' argument that "absent recognition of the problems addressed by the claimed formulations, one of skill in the art could not arrive at the claimed formulations absent hindsight in view of the advantages identified by the Applicants", the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the teaching of Azrolan that a preferred formulation of CCI-779 is taught by Waranis would clearly motivate one of skill in the art to combine the references. Additionally, common knowledge of one of skill in the art would motivate them to determine a suitable preservative/stabilizer for a parenteral formulation, and the teachings of Haeberlin provide such an agent.

The rejection of instant Claims 12-21 under 35 USC §103 is maintained.

Conclusion

15. Claims 12-21 are rejected.

16. No claims are allowed.

17. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregg Polansky whose telephone number is (571) 272-9070. The examiner can normally be reached on Mon-Thur 8:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GP

Phyllis Spivack 2/11/07

PHYLLIS SPIVACK
PRIMARY EXAMINER